by arclightshroom

SYNTHESIS OF GHB AND METHAQUALONE

This work describes the synthesis of two gabaergic drugs; GHB and methaqualone. Despite its synthetic accessibility and seemingly high popularity, methaqualone remains a remarkably uncommon compound in the black market—making it a fascinating piece to add to the collection of any drug hobbyist.
In contrast, the easily synthesized or otherwise easily obtained compound GHB has become quite popular in the drug scene. Due to its synthesis being well known and its pharmacological similarities with the more synthetically and culturally fascinating methaqualone, it was decided to cover both topics together.

Synthesis of GHB through Sandmeyer reaction

30.9g of GABA and 20.7g of $NaNO_2$ were dissolved in 70mL of water with stirring and cooled in an ice bath to approx. 0-5°C , after which HCl (33.5mL, 32%) was added dropwise at a slow enough rate to keep the temperature around 5°C. Once the addition was completed a little more hydrochloric acid was added to bring the pH down to 1-2, the ice bath removed and the mixture stirred for 24h at room temperature. The reaction mixture was then saturated with sodium chloride and extracted with 5x20mL DCM, the organic extracts were dried over sodium sulfate and desolventized to yield GBL as a yellowish liquid. The residue is then distilled under vacuum yielding 19.35g of almost clear GBL, which was added dropwise to a solution of sodium hydroxide in ethanol (9g NaOH in 50mL EtOH, a 2-3mL of water added to help dissolve the hydroxide) with stirring. The resulting orange solution is refluxed for 15 minutes, NaGHB precipitates out on cooling and it's collected by filtration. The mass is then washed with ice cold ethanol, melted at 150°C and poured in a large beaker, where it solidifies as a white wax. Final yield 23.5g, about 75%.

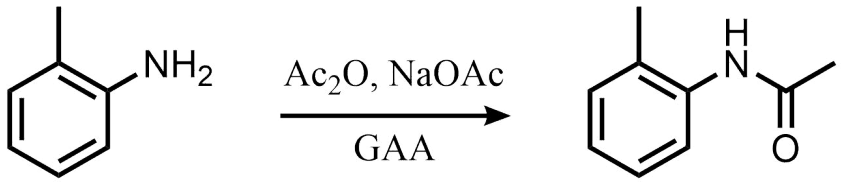
NOTES: Temperature control is essential to avoid the production of nitrogen dioxide, a toxic brown gas.
GBL has a fairly good solubility in water, saturating the reaction mixture with salt helps pushing it into the DCM. An alternative workup involves steam distillation, the distillate has a GBL concentration of approx. 1g/10mL, and it can be converted to NaGHB by treatment with equimolar sodium bicarbonate or sodium hydroxide.
A yellow impurity is formed that follows the GBL even with distillation, the bulk of it is removed with the final ethanol crystallization and washings, which proved much more effective than treatment with activated carbon.

NaGHB cake collected on the filter

NaGHB vax after being melted

Synthesis of methaqualone

Acetylation reaction:

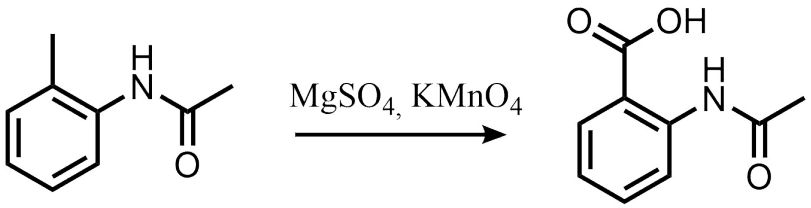


10mL o-toluidine and 500mg sodium acetate are dissolved in 10mL GAA, then 20mL of acetic anhydride are added in portions and the mixture stirred at room temperature for 1 hour. The solution is then dumped in cold water and filtered, yielding 12.31g of o-acetyltoluidine. The yield is almost quantitative. M.p: ~110°C

NOTE: Addition of acetic anhydride is very exothermic, adding it dropwise is not necessary, but adding it all at once may cause a violent reaction. I added it in 5mL portions with 20-30 seconds in between.

Dry product. No further purification is needed

Oxidation reaction:

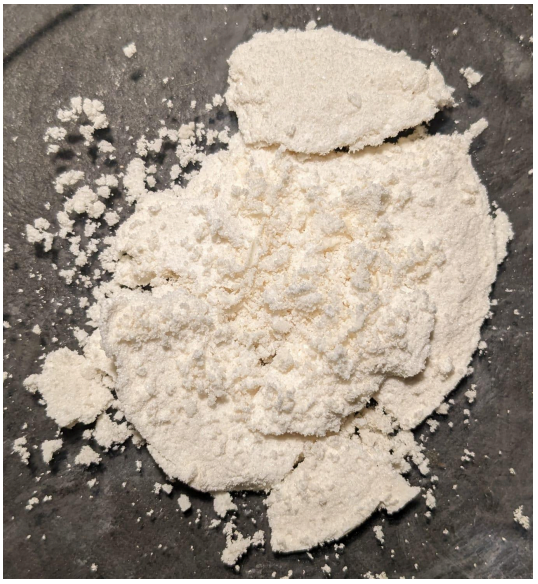


12g of o-acetyltoluidine are suspended with stirring in 300mL of water, 24.9g of $MgSO_4$ are added and the mixture heated to 75°C. When at temperature, 35.3g of potassium permanganate are added in small portions to keep the temperature between 85-95°C, after the addition has been completed the mixture is kept at 85°C for 2h. The liquid is vacuum filtered while still hot, and the filtrate acidified on cooling with 20% sulfuric acid. Acetylanthranilic acid precipitates on cooling and it's recovered by filtration in a 85% yield, dry weight 12.4g. M.p: ~185°C

NOTE: The original procedure I've found used 600mL for 5g o-acetyltoluidine, which was way too much. I suspect that the solvent volume could be further decreased, but mechanical overhead stirring might be necessary then.

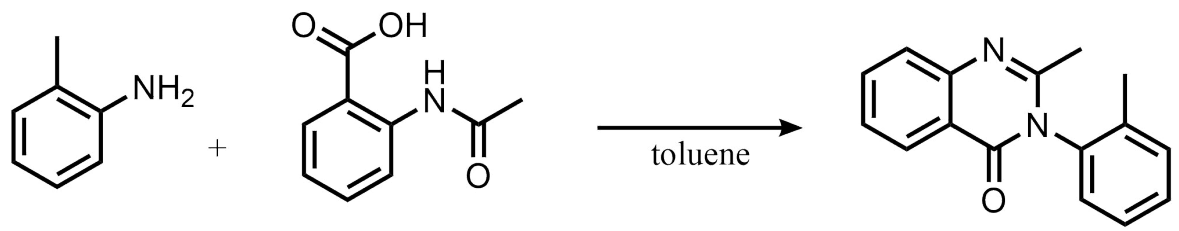
Addition of $KMnO_4$ is exothermic on delay, and reacts quickly to form manganese dioxide precipitate. I found it to be very effective (and safer) to add the permanganate slowly and carefully to avoid aggressive boiling and MnO_2 clogging. This could be probably avoided by using a large amount of water (120mL/g), but I prefer working with smaller volumes.

MnO_2 stuck on glass can be cleaned with HCl, carefully, as the reaction generates chlorine gas. Water soluble MnCl2 is toxic and must be disposed of properly.



Dry product. No further purification is needed

Condensation reaction:



4.63g of acetylanthranilic acid and 2.7g of o-toluidine are dissolved in 20mL toluene and refluxed with a Dean–Stark apparatus for an hour. The trap is then drained of both water and toluene and the heat is increased to 170-180°C, allowing the reaction mixture to run dry. The liquid residue is stirred at 180°C for 1.5h, or until no more water vapor evolves. The orange residue is redissolved in 20mL toluene and quickly extracted with 3x20mL 10% HCl, the acidic extracts solidify into a chunk of methaqualone HCl after swirling it around. The salt is then redissolved in boiling water and freebased with sodium hydroxide. The sticky freebase is dried under vacuum and dissolved in acetone, methaqualone HCl is precipitated by dripping in conc. hydrochloric acid while swirling the beaker, it is then suspended in refluxing acetone for 15 minutes, filtered, washed with more acetone and dried to give 3.5g of clean product in a 47% yield.

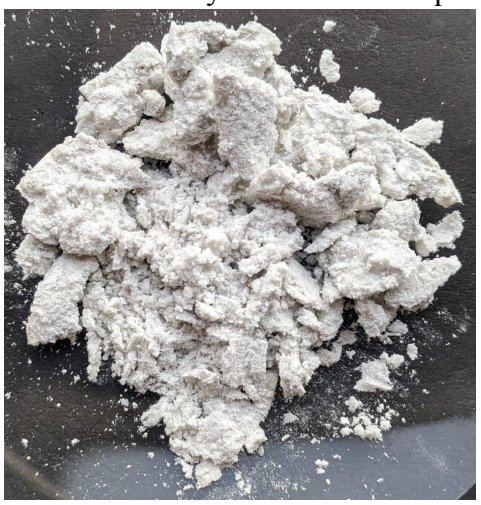
Orange residue after reacting Crude methaqualone HCl

NOTE: The reaction can be done by mixing acetylanthranilic acid and o-toluidine solvent free and heating directly to 180°C, but I had better results doing it gradually. Toluidine is added in a 1:1 molar ratio, and it's not enough to dissolve the acid, giving a thick slurry that is difficult to stir and heat homogeneously, especially on a larger scale it ends up with a lot of tar.

Adding excess o-toluidine is a very bad idea, it sticks to the freebase making it impossible to clean. If the HCl salt oils out in acetone instead of giving a crystalline solid and the freebase has the consistency of glue (normal to some degree, especially if wet) then there's a lot of toluidine. Traces of toluidine can be removed by washing methaqualone HCl with cold water, as it's poorly soluble in it contrary to o-toluidine HCl.

Don't be fooled by the white appearance of crude methaqualone HCl, it needs extensive cleaning. It looks white but the first acetone washings of it are bright red.

The reaction is low yielding (47%), but I'm personally content with it as the synthesis is overall very cheap and easy. Yields of 80% can supposedly be achieved with phosphoryl chloride, but I would consider it worth it only for commercial production.



Clean methaqualone HCl

TLC ANALYSIS: Eluent DCM:EtOH:NH_3 (conc.) 1:1:0.1. Visualized with $KMnO_4$ stain

I made up this solvent system, and it doesn't work quite well. Lots of streaking and poor separation, but unfortunately I wasn't able to find any TLC data in literature for these compounds.
AT: O-acetyltoluidine, Rf: 0.73
AA: Acetylanthranilic acid, Rf: 0.81
MQ: Methaqualone freebase, Rf: 0.94

Sources:

1) Sandmeyer reaction of GABA to GBL/GHB
https://erowid.org/archive/rhodium/chemistry/gaba2ghb.html

2) https://prepchem.com/synthesis-of-anthranilic-acid/

3) Soliman, F. S. G., Shafik, R. M., & Elnenaey, E. A. (1978). Synthesis of Methaqualone and Its Diphasic Titration in Pure and Tablet Forms. In Journal of Pharmaceutical Sciences (Vol. 67, Issue 3, pp. 411–413). Elsevier BV. https://doi.org/10.1002/jps.2600670339